Multiple Myeloma Highlights From the 2022 American Society of Hematology (ASH) Annual Meeting

December 20, 2022

Tech Support

1-719-234-7952
Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation
  - Exhibit Hall

Submit your questions throughout the program!
The Work of the MMRF

The MMRF does three things in relentless pursuit of its mission to accelerate a cure for each and every myeloma patient.

1. We accelerate new treatments
   Bringing next-generation therapies to patients faster

2. We drive precision medicine
   Using data to deliver better answers and more precise treatments for patients

3. We empower patients
   Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

MMRF CoMMpass Study: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma
- Goals
  - Learn which patients respond best to which therapies
  - Identify new targets and new hypotheses
- Newly diagnosed patients will be followed for at least 8 years

All participants undergo a type of detailed genetic testing called *genomic sequencing*. 
CoMMpass Is a Trial of Discovery

- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - Drive multiple myeloma cell growth and survival
      - Contribute to drug resistance
      - May predict which patients respond to which therapy
    - Genetic abnormalities that help refine risk assessment
  - Led to conception of the MyDRUG trial

All patients in CoMMpass had genomic sequencing from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!
How does the MMRF CureCloud work?

1. Sign up on the MMRF CureCloud website or in person at a CureCloud participating clinic and see if you are eligible.
2. Convenient at-home blood test. A medical professional will come to you.
3. Medical record collection. Provide your myeloma doctors and we’ll contact them.
4. Personalized insights. Learn more about your myeloma.
5. Discuss with your doctor.

You’ll get a blood test at home.
- After you sign up, you will receive a CureCloud bloodwork kit.
- A trained medical professional will come to your home to draw your blood.

We’ll collect your medical records.
- When you sign up, you’ll provide the names and contact information for the doctors who have treated your myeloma and any clinics or hospitals where you’ve had tests (bone scans, MRI, etc.).
- We’ll contact them and collect your records.

What happens to my information?

Your information is shared anonymously — to help the entire myeloma community. The information you contribute is made anonymous and will be available to the myeloma community. Researchers will be able to use this information to learn more about myeloma, helping to find new medicines or even, someday, a cure. In the future, patients and their doctors will be able to access this data to find specific treatment options that are right for them.

You’ll learn more about your myeloma.
Once we’ve collected your medical records, you’ll have access to a private, personal dashboard with all the medical information related to your myeloma*.

With all your information at hand, you’ll be able to have better conversations with your myeloma care team.

*Information will only be collected from the myeloma doctors you provide when you sign up.
A Patient's Own Data—Compared With Data From Many Others

- Clinical data with patient's data represented (green diamond)
- Patient can filter data by characteristics like age, sex, and race to see patients like themselves
A Patient's Own Data—Compared With Data From Many Others

- Clinical data with patient's data represented (green diamond)
- Patient can filter data by characteristics like age, sex, and race to see patients like themselves

A Patient's Own Data—Compared With Data From Many Others

- Treatment data with patient's data represented (green diamond)
- Patient can filter data by characteristics like age, sex, and race to see patients like themselves

© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.
Thank you

Speakers

Malin Hultcrantz, MD PhD
Memorial Sloan Kettering Cancer Center
New York, New York

Joshua R. Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York
Multiple Myeloma Highlights From the 2022 American Society of Hematology (ASH) Annual Meeting
December 20, 2022

Topics To Discuss

Precursor Conditions and Disease Monitoring
- iStopMM study and MGUS observations
- Treating high-risk SMM
- Mass spectrometry as a new measurement tool

Updates on Newly Diagnosed MM
- Frailty
- High risk disease
- Maintenance therapy

Updates on Relapsed/Refractory MM
- Current CAR T-cell therapy
- Isatuximab-based therapies
- Bispecific antibodies
- New drugs on horizon

Updates on Precursor Conditions, Monitoring, and Newly Diagnosed Multiple Myeloma

Malin Hultcrantz, MD, PhD
Memorial Sloan Kettering Cancer Center
New York, New York

17

18
Nationwide Screening Studies to Identify Patients With Myeloma Precursor Conditions

Iceland

iStopMM Study
148,704 individuals 40 years of age or older in Iceland enrolled
75,422 screened for M protein and abnormal free light chain
3,358 individuals with MGUS

United States and Canada

THE PROMISE STUDY

Learning More About MGUS

MGUS subtypes: 57% IgG; 21% IgM; 12% IgA. IgA prevalence rises slowly with age and plateaus after age 70.

Risk categories*: 43% low; 40.4% low-intermediate; 16.3% high-intermediate; and 0.3% high.

No evidence of MGUS progression following SARS-CoV-2 vaccination (in 1,814 individuals vaccinated) irrespective of the number of doses administered and the type of vaccine used.†

3.9% of individuals screened have MGUS (5% in individuals over 50 years of age)

iStopMM data set used to create a prediction model to identify patients with MGUS that have ≥10% bone marrow plasma cells. This model may help clinicians determine which of their MGUS patients may defer a bone marrow biopsy.‡

*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma:
(1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow.

Therapeutic Intervention for High-Risk SMM

Risk of progression to active myeloma:
- High-risk SMM: 50% in 2 years
- SMM: 10% per year
- High-risk MGUS: 1% per year

High-risk MGUS
- Non-IgG M protein
- Abnormal serum free light chain ratio
- M protein >1.5 g/dL

SMM
- Current standard of care is to observe only for low- and intermediate-risk patients.

High-risk SMM
- BM plasma cells >20%
- M protein >2 g/dL
- FLC ratio >20
**Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex for High-Risk SMM Patients**

**GEM-CESAR Study**

High-risk* smoldering multiple myeloma patients

- **Induction**: Kyprolis + Revlimid + dex (KRd)
- **Consolidation**: KRd
- **Maintenance**: Revlimid

90 patients

At 70 months, 94% of patients have not progressed to multiple myeloma; 48% have biochemically progressed (rescue therapy with DPd resulted in 80% overall response rate)

The presence of SLiM criteria and MRD at the end of maintenance predicted progression.

The achievement of MRD negativity after maintenance and 4 years after ASCT predicted sustained MRD negativity.

Encouraging results for a curative approach to high-risk SMM.

*According to the Mayo and/or Spanish models.

---

**Four-Drug Combination Strategy for High-Risk SMM Patients**

**ASCENT Study**

High-risk* smoldering multiple myeloma patients

- **Induction**: Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)
- **Consolidation**: Dara-KRd
- **Maintenance**: Darzalex + Revlimid

87 patients

Best overall response rate was 97% (92% ≥VGPR); 84% of patients achieved MRD negativity.

Grade ≥3 hematologic toxicity in 18% of patients; non-hematologic toxicity in 51% of patients.

89.9% of patients are progression-free at 3 years.

High response rates with a transplant-free regimen. Longer follow up will answer possible cure with early intervention.

*Based on the 2/2020 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow; or a total score of ≥9 on IMWG scoring system.
Multiple Myeloma Highlights From the 2022 American Society of Hematology (ASH) Annual Meeting
December 20, 2022

Disease Monitoring

Mass Spectrometry

Minimal Residual Disease Detection and Monitoring in the Blood by Mass Spectrometry

MRD is currently measured using a bone marrow sample; myeloma cells are detected using one of two methodologies: (1) flow cytometry or (2) next-generation sequencing.

Mass spectrometry (MS) is being evaluated as a method to assess MRD or M protein in the blood as a potentially more sensitive test to detect MRD in patients after therapy.

The phase 3 trials GEM2014MAIN and GMMG-MM5 are providing critical information on the use of this new technology compared to results from bone marrow biopsy samples.¹-³

Sustained MRD negativity as determined by MS is prognostic for improved outcome, whereas MRD positivity is associated with worse outcome and is a potential marker for earlier treatment intervention.⁴

MS is more sensitive than measuring the M-spike (SPEP and IFE)

MS has a high concordance with bone marrow based MRD methods and can guide the need for bone marrow biopsies

Newly Diagnosed Multiple Myeloma

Exploring Frailty


Newly diagnosed myeloma patients ≥65 years receiving novel drugs between 2007–2014 identified

<table>
<thead>
<tr>
<th>Frailty Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-frail</td>
<td>5%</td>
</tr>
<tr>
<td>Prefrail</td>
<td>25%</td>
</tr>
<tr>
<td>Mildly frail</td>
<td>32%</td>
</tr>
<tr>
<td>Moderately frail</td>
<td>23%</td>
</tr>
<tr>
<td>Severely frail</td>
<td>16%</td>
</tr>
</tbody>
</table>

Frailty status followed for 3 years

Frailty categorization changed in 93% of patients (78% improved, 72% deteriorated)

Current frailty status was a better predictor of overall survival than frailty at diagnosis.

*Frailty categorization changes during myeloma disease course, necessitating the need for re-measurement.*
### Dexamethasone-Sparing Regimen for Frail Patients

**IFM2017-03 Trial**

<table>
<thead>
<tr>
<th>Newly diagnosed myeloma patients (≥65 years old) with IFM frailty score ≥2</th>
<th>Deeper responses observed with RD vs Rd at 4, 8, and 12 months (≥VGPR rates 41% vs 26%; 68% vs 48%; 71% vs 55%, respectively).</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 patients</td>
<td>Favorable safety profile without increased infection or pneumonia with RD vs Rd</td>
</tr>
<tr>
<td>Revlimid + Darzalex (RD)</td>
<td>Encouraging results for a dexamethasone-sparing strategy for frail multiple myeloma patients.</td>
</tr>
<tr>
<td>95 patients</td>
<td></td>
</tr>
</tbody>
</table>


---

**Newly Diagnosed Multiple Myeloma**

**High-Risk Disease**
**High-Risk Disease Definitions**

**Revised International Staging System (R-ISS)**

- **R-ISS Stage I**
  - ISS stage I
  - Serum β2M level <3.5 mg/L
  - Serum albumin level ≥3.5 g/dL
  - No high-risk CA*
  - Normal LDH level

- **R-ISS Stage II**
  - All other possible combinations

- **R-ISS Stage III**
  - ISS2 stage III
  - Serum β2M level ≥5.5 mg/L
  - High-risk CA* or high LDH level

**Mayo Clinic Stratification for Myeloma & Risk-Adapted Therapy (mSMART)**

- **High risk**
  - Genetic abnormalities*
    - t(4;14)
    - t(14;16)
    - t(14;20)
    - del 17p
    - p53 mutation
    - Gain 1q
  - R-ISS Stage 3
  - High plasma cell S-phase
  - GEP: high-risk signature
  - Double-hit myeloma: any two high-risk genetic abnormalities
  - Triple-hit myeloma: three or more high-risk genetic abnormalities

- **Standard risk**
  - All others including:
    - Trisomies
    - t(11;14)
    - t(6;14)

**Additional Features**

- **Disease features**
  - Other cytogenetic and genetic abnormalities
  - Plasma cell leukemia
  - Extramedullary disease
  - Renal failure

- **Patient features**
  - Comorbidities
  - Frailty

- **Response features**
  - Lack of response to therapy
  - Short first PFS

---

*Deletion 17p and/or t(4;14) and/or t(14;16)*


**Treatment Regimens for High-Risk Disease Features**

**Kyprolis-Revlimid-dex (KRd) vs Revlimid-Velcade-dex (RVd) Retrospective Chart Review**

- 154 consecutive high-risk* newly diagnosed myeloma patients treated with KRd (n=87) and VRd (n=67) at Memorial Sloan Kettering Cancer Center from 2015 to 2019
- Patients receiving KRd vs RVd had:
  - Greater depth of response
  - Significant improvement in PFS (especially those who received early ASCT)
  - R-ISS stage II and III (compared to stage I) were significant predictors for progression or death
  - More than 6 cycles of treatment was associated with longer PFS and OS

- **OPTIMUM Study**
  - Study to evaluate the efficacy of Darzalex-cyclophosphamide-Velcade-Revlimid-dex (Dara-CyVRd) induction followed by ASCT and 2 rounds of consolidation with Dara-VR (with or without dex) in 107 ultra high-risk† patients with multiple myeloma and plasma cell leukemia (PCL)
  - By end of second consolidation, 46.7% of patients were MRD negative (10⁻⁵); 84% of patients who were MRD negative after ASCT sustained their MRD negativity at the end of second consolidation
  - 86% of patients were alive and 77% were progression free at 30 months


---

*High risk cytogenetic abnormalities defined as 1q+ (gain or amp), t(4;14), t(14;16), t(14;20), and/or del(17p) or monosomy 17.

†≥2 high risk lesions: t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p), or SKY92 risk signature.
### Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

#### GMMG-CONCEPT Study

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa + Kyprolis + Revlimid + dex (Isa-KRd)</td>
<td>ASCT</td>
<td>Isa-KR</td>
</tr>
</tbody>
</table>

**Best Response (through consolidation), %**

<table>
<thead>
<tr>
<th></th>
<th>Transplant Eligible (n=99)</th>
<th>Transplant Ineligible (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>94.9</td>
<td>88.5</td>
</tr>
<tr>
<td>sCR/CR</td>
<td>72.7</td>
<td>57.7</td>
</tr>
<tr>
<td>VGPR</td>
<td>18.2</td>
<td>30.8</td>
</tr>
<tr>
<td>PR</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MRD negative ((1 \times 10^{-5})) in evaluable patients</td>
<td>67.7</td>
<td>54.2</td>
</tr>
</tbody>
</table>

#### Adverse Events, % Grade \(\geq 3\)

<table>
<thead>
<tr>
<th></th>
<th>Transplant Eligible (n=97)</th>
<th>Transplant Ineligible (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39.2</td>
<td>28</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24.7</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26.8</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.4</td>
<td>12</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>27.8</td>
<td>28</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2.1</td>
<td>20</td>
</tr>
</tbody>
</table>

Total population cytogenetic abnormalities:
- 44% del(17p); 38.4% t(4;14); 15.2% t(14;16); 36% >3 copies of 1q21; 30.4% ≥2 high-risk cytogenetic abnormalities


#### RADAR Study

**Transplant eligible newly diagnosed multiple myeloma**

- **Standard-risk patients**
  - n=1,120
  - R-CyBorD
  - Isa
  - ASCT
- **High-risk\* patients**
  - n=280
  - Isa-R-CyBorD

**MRD negative**

- Isa
- R
- Isa-RVd (x 4) + Isa-R

**MRD positive**

- Isa
- R
- R + Isa
- Isa-RVd (x 4) + Isa-R

**Innovative study design to tailor treatment:**
- Deescalate for MRD neg patients
- Deepen response for MRD positive patients
- Manage ultra-HR disease

*At least 2 of t(4;14), t(14;16), del(17p), 1q+, 1p-; Yong K et al. Blood. 2022;140. Abstract 762.*
Newly Diagnosed Multiple Myeloma

Maintenance Therapy

Maintenance Duration

Myeloma XI Study

Newly diagnosed myeloma patients

Induction

CTD/CRD

KCRD

Consolidation

CVD

No CVD

ASCT

Maintenance

730 patients

518 patients

Revlimid

Observation


<table>
<thead>
<tr>
<th>At Time of Randomization to Maintenance Therapy (median follow up 44.7 mos)</th>
<th>All Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mos)</td>
<td></td>
</tr>
<tr>
<td>Revlimid</td>
<td>64</td>
</tr>
<tr>
<td>Observation</td>
<td>32</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.52</td>
</tr>
<tr>
<td>P Value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*PFS benefit across all patient subgroups on Revlimid maintenance therapy: standard risk; molecular high risk which included the presence of del(17p), gain(1q), t(4:14), t(14:16), or t(14:20); MRD positive; and MRD negative.

More evidence for the benefit of longer duration of Revlimid maintenance in patients who are MRD positive than MRD negative. And evidence of ongoing benefit beyond 2–3 years for patients with both standard- and high-risk disease.
Second Primary Malignancies With Revlimid

**Myeloma XI Study**

- **Transplant eligible:**
  - 730 patients
  - 5.5% developed an SPM overall
  - SPM incidence was 12.2% at 7 years in lenalidomide maintenance arm compared to 5.8% in the observation arm

- **Transplant ineligible:**
  - 518 patients
  - 9.9% developed an SPM overall
  - SPM incidence was 17.1% at 5 years in lenalidomide maintenance arm compared to 10% in the observation arm

Double-exposure to lenalidomide (induction and maintenance) is associated with higher incidence of SPM and is more marked in transplant-ineligible patients.

Using MRD Negativity to Guide Discontinuation of Maintenance Therapy

**MRD2STOP Study**

<table>
<thead>
<tr>
<th>Complete response × 2 years and/or MRD negative (≤10⁻⁵), PET-negative, 1+ years maintenance</th>
<th>Discontinue maintenance</th>
<th>Continue maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD and PET/CT negative N=38</td>
<td>MRD and PET/CT positive</td>
<td></td>
</tr>
<tr>
<td>Discontinue maintenance</td>
<td>Continue maintenance</td>
<td></td>
</tr>
</tbody>
</table>

- 89% remain on study (5% with PD, 6% withdrew).
- MRD resurgence occurred in 13% of patients (2 patients had resurgence of M-protein and disease progression).
- MRD negativity (at 10⁻⁶ and 10⁻⁷) is sustained even after discontinuation of maintenance therapy.

MRD-guided discontinuation of maintenance may carry significant cost savings.

*MRD assessment performed with PET, flow cytometry (10⁻⁵), next-generation sequencing (10⁻⁶), and CD138-selected next-generation sequencing (10⁻⁷)*

## Key Points

1. **MGUS from the iStopMM trial:** 3.9% of individuals over the age of 40 years. The majority of individuals have low risk of progression.

2. Mass spectrometry is being evaluated as a blood-based method for disease monitoring.

3. Trials designs for high-risk smoldering and multiple myeloma show promising results.

4. Individualizing maintenance therapy based on MRD monitoring.

5. Focus on frailty and quality of life.

## Questions & Answers
Updates on Relapsed/Refractory Multiple Myeloma

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

Relapsed/Refractory Multiple Myeloma
Sarclisa Combinations
### Sarclisa After Early or Late Relapse

**IKEMA Study**

Patients with relapsed/refractory myeloma who received 1-3 prior therapies, no prior therapy with Kyprolis and not refractory to prior anti-CD38 antibody

<table>
<thead>
<tr>
<th></th>
<th>Early Relapse</th>
<th>Late Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>24.7</td>
<td>42.7</td>
</tr>
<tr>
<td>Kd</td>
<td>17.2</td>
<td>21.9</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>82</td>
<td>90.4</td>
</tr>
<tr>
<td>≥VGPR rate (%)</td>
<td>67.2</td>
<td>76</td>
</tr>
<tr>
<td>MRD negativity rate (%)</td>
<td>24.6</td>
<td>37.5</td>
</tr>
<tr>
<td>MRD-negative CR rate (%)</td>
<td>18</td>
<td>30.8</td>
</tr>
</tbody>
</table>

Data evaluated according to patients who experienced an early* versus late† relapse.

Regardless of early or late relapse, RRMM patients benefit from the use of isa-Kd with respect to depth of response and prolonged PFS.

*<12 months from initiation of most recent line of therapy (for patients who had ≥2 lines of therapy); <18 months (for patients who had 1 prior line of therapy) and <12 months from ASCT
†≥12 months from initiation of most recent line of therapy (for patients who had ≥2 lines of therapy; ≥18 months for patients who had 1 prior line of therapy)


### Relapsed/Refractory Multiple Myeloma

**CAR T-Cell Therapy: How It’s Going**
**CAR T-Cell Therapy**

Genetically modified T cells designed to recognize specific proteins on myeloma cells

CAR T cells are activated once in contact with the myeloma cell and can destroy the myeloma cell

CAR T cells can persist for long periods of time in the body

CAR T cells are created from a patient’s own blood cells, but the technology is evolving to develop “off-the-shelf” varieties (allo-CART)

CAR, chimeric antigen receptor; MM, multiple myeloma


---

**CAR T-Cell Therapy Insights**

**Prognostic Value of Depth of Response Following CAR T-Cell Therapy**

- Achieving sustained, undetectable MRD after Abecma is associated with prolonged PFS
- Only MRD status—not complete response (CR) status—predicted early relapse 1 month after Abecma.
- However, both MRD and CR status at 12 months were required to identify patients with longer PFS

---

**Real-World Outcome With Abecma After BCMA-Targeted Therapy**

- Eleven US academic centers conducted a retrospective analysis on the real-world outcome for patients treated with Abecma after previously receiving BCMA-targeted therapy
- Prior BCMA-targeted treatment is associated with inferior PFS and a trend toward inferior outcomes for patients receiving Abecma within 6 months of having received prior BCMA-targeted therapy
- Warrants further investigation into the optimal timing of Abecma infusion

---

**Outcomes and Options Following Relapse From CAR T**

- A retrospective analysis of 78 patients with RRMM who received BCMA-targeted CAR T-cell therapy
- Patients who had previously been refractory to a specific drug class re-responded after CAR-T relapse
- Median OS after progressing on CAR T was 14.8 months and 18 months for patients who received subsequent BCMA CAR T or BCMA bispecific antibodies within 6 months of progressing on CAR T

---

**Assessment of Cytopenias from CAR T**

- Retrospective review of data from 90 patients 4 months after CAR T-cell infusion
- Patients with poor hematologic recovery (28%) compared with adequate recovery (72%) were older, more heavily pretreated, and more likely to have received ≥1 ASCT

**Abecma in Earlier Lines of Treatment**

- KarMMa-2 phase 2 multicenter study of Abecma in 37 patients with RRMM with high-risk disease
- Results show a benefit to Abecma in earlier line of treatment

---


---

*Early relapse after frontline therapy or inadequate response after frontline ASCT*
Relapsed/Refractory Multiple Myeloma

Bispecific Antibodies

Bispecific antibodies are also referred to as dual-specific antibodies, bifunctional antibodies, or T-cell-engaging antibody.

Bispecific antibodies can target two cell surface molecules at the same time (one on the myeloma cell and one on a T cell).

Many different bispecific antibodies are in clinical development.

Availability is off-the-shelf allowing for immediate treatment.

Examples:
- Tecvayli (teclistamab)
- Elranatamab
- TNB-303B (ABBV-383)
- Linvoseltamab
- Cevostamab
- Talquetamab

Multiple Myeloma Highlights From the 2022 American Society of Hematology (ASH) Annual Meeting
December 20, 2022

Bispecifics Discussed at ASH

<table>
<thead>
<tr>
<th>Bispecific Antibody</th>
<th>Target (on MM cell × T cell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecvayli (teclistamab)</td>
<td>BCMA × CD3</td>
</tr>
<tr>
<td>Elranatamab</td>
<td>BCMA × CD3</td>
</tr>
<tr>
<td>Linvoseltamab</td>
<td>BCMA × CD3</td>
</tr>
<tr>
<td>Alnuctamab</td>
<td>BCMA × CD3</td>
</tr>
<tr>
<td>ABBV-383</td>
<td>BCMA × CD3</td>
</tr>
<tr>
<td>Talquetamab</td>
<td>GPRC5D × CD3</td>
</tr>
<tr>
<td>Forimtamig (RG6234)</td>
<td>GPRC5D × CD3</td>
</tr>
<tr>
<td>Cevostamab</td>
<td>FcRH5 × CD3</td>
</tr>
</tbody>
</table>

GPRC5D, G protein-coupled receptor family C group 5 member D

Bispecific Antibody Target (on MM cell × T cell)

Tecvayli in Combination With Darzalex and Revlimid

Phase 1b study (MajesTEC-2) in RRMM with 1–3 prior lines of therapy (including an IMiD and a PI).

32 patients—who had received at least 2 prior lines of therapy—received treatment with the triplet with Tecvayli at 2 different doses (0.72 mg/kg and 1.5 mg/kg) subcutaneously.

Most Frequent Non-Hematologic Adverse Events, %

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>81.3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Infections (≥1)</td>
<td>90.6</td>
<td>37.5</td>
</tr>
<tr>
<td>COVID-19</td>
<td>37.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>31.3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25</td>
<td>15.6</td>
</tr>
<tr>
<td>COVID pneumonia</td>
<td>12.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Pneumonia pseudomonal</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>CMV</td>
<td>6.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

IMiD, immunomodulatory drug; PI, proteasome inhibitor

**Elranatamab in Patients With Relapsed/Refractory Multiple Myeloma**

### Updated Efficacy and Safety Results with Elranatamab

**Phase 1 study in RRMM (91% triple-class refractory)**

<table>
<thead>
<tr>
<th>Response</th>
<th>% Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>27.3</td>
</tr>
<tr>
<td>VGPR</td>
<td>18.2</td>
</tr>
<tr>
<td>CR</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Median duration of response 17.1 months.

**Phase 2 study in RRMM refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody—no prior BMCA-targeted treatment**

<table>
<thead>
<tr>
<th>Response</th>
<th>% Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>61%</td>
</tr>
<tr>
<td>VGPR</td>
<td>13</td>
</tr>
<tr>
<td>CR</td>
<td>14.6</td>
</tr>
<tr>
<td>sCR</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Elranatamab to be investigated alone and in combination with other drugs in phase 3 studies.

IMiD, immunomodulatory drug; PI, proteasome inhibitor


---

**Phase 1 Study of Alnuctamab in Patients With Relapsed/Refractory Multiple Myeloma**

### Intravenous Formulation Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IV Alnuctamab (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up (months)</td>
<td>8.0</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>39</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>33.6</td>
</tr>
<tr>
<td>Responses ongoing (%)</td>
<td>48</td>
</tr>
<tr>
<td>Median progression-free survival (months)</td>
<td>3.1</td>
</tr>
</tbody>
</table>

### Subcutaneous Formulation Results

<table>
<thead>
<tr>
<th>Response</th>
<th>% Responding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>53%</td>
</tr>
<tr>
<td>VGPR</td>
<td>41%</td>
</tr>
<tr>
<td>CR</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Most Frequent Adverse Events, %**

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>37</td>
<td>32</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>34</td>
<td>9</td>
</tr>
<tr>
<td>ICANS</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ALT increase</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

**Talquetamab in Patients With Relapsed/Refractory Multiple Myeloma**

**Phase 1/2 study (MonumenTAL-1) in RRMM**

288 patients—with no prior T-cell redirecting therapies—received treatment with talquetamab at 2 different doses (0.4 mg/kg every week and 0.8 mg/kg every other week) subcutaneously.

Data from this trial was recently used to submit a Biologics License Application to the U.S. Food and Drug Administration for the treatment of patients with relapsed or refractory multiple myeloma.

<table>
<thead>
<tr>
<th>Most Frequent Adverse Events, %</th>
<th>0.4 mg/kg</th>
<th>0.8 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>44.8</td>
<td>31.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34.3</td>
<td>30.8</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>28</td>
<td>25.9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27.3</td>
<td>20.3</td>
</tr>
<tr>
<td>Infections</td>
<td>57.3</td>
<td>16.8</td>
</tr>
</tbody>
</table>

IMiD, immunomodulatory drug; PI, proteasome inhibitor


---

**Forimtamig (RG6234) in Patients With Relapsed/Refractory Multiple Myeloma**

**Phase 1 study in RRMM**

105 patients received treatment with RG6234 in 2 different formulations (intravenous and subcutaneous).

Expected Toxicities With T-Cell Activating Therapies (CAR T and Bispecific Antibodies)

- **Cytokine release syndrome (CRS)**
  - Usually occurs within first 1–2 weeks
  - Frequency (all grade and grade 3–5) higher with CAR T

- **Infections**
  - Viruses: CMV, EBV
  - PCP/PJP
  - Ongoing discussions regarding prophylactic measures
    - IVIG
    - Anti-infectives

- **Cytopenias**

- **Neurotoxicity (ICANS)**
  - Usually occurs within first 1–2 weeks
  - Frequency (all grade and grade 3–5) higher with CAR T

- **Off target effects (with GPRC5D targeted agents)**

**ICANS**, immune effector cell-associated neurotoxicity syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCP/PJP, pneumocystis pneumonia/pneumocystis jiroveci pneumonia

Pretreatment With Tocilizumab Reduces Incidence and Severity of Cytokine Release Syndrome

- **Cevostamab is an FcRH5-targeted bispecific antibody under investigation in patients with RRMM.**
- **An ongoing phase 1 study evaluating the use of tocilizumab (an IL-6 antibody) prior to the first dose of cevostamab. A single 8 mg/kg dose of tocilizumab was administered to 28 patients 2 hours prior to cevostamab.**

- **35.7% of patients receiving tocilizumab experienced CRS compared to 90.9% of patients who didn’t receive tocilizumab.**

- **Grade 3 CRS was observed in only one patient in each group and no G4/5.**

- **The frequency of neutropenia was higher for patients receiving tocilizumab compared with those who didn’t (64.3% vs 38.6% G3/4).**

- **No impact on response was observed with tocilizumab pretreatment.**

Fixed-Duration Therapy With Bispecifics Cevostamab

At the time of this presentation, no patients who achieved an sCR have relapsed!


Relapsed/Refractory Multiple Myeloma

Drugs on the Horizon
What’s next for CAR T-cell therapy?

### BMS-986354[^1]
- **Features**
  - Targets BCMA with a shortened manufacturing time through the NEXT-T process
- **Trial Details**
  - Phase 1 trial of 55 patients with RRMM with a median of 5 prior lines of therapy
- **Clinical Results**
  - CRS occurred in 80% of patients with only 1 patient experiencing ≥G3.
  - Neurotoxicity occurred in 10.9% of patients (one grade 4).
  - Overall response rate was 98.1% with 57.4% achieving ≥VGPR (29.6% ≥CR).

### FasT CAR-T GC012F[^2]
- **Features**
  - Targets BCMA and CD19
  - Manufacturing process that takes as little as 24 hours
- **Trial Details**
  - Phase 1 trial of 13 newly diagnosed high-risk MM patients ineligible for stem cell transplant
- **Clinical Results**
  - 100% of patients achieved ≥VGPR (69% sCR)
  - All patients achieved MRD negativity (by EuroFlow).
  - CRS observed in 23% of patients (all low grade).

### BMS-986393[^3]
- **Features**
  - Targets GPRC5D
- **Trial Details**
  - Phase 1 trial of 17 heavily pretreated patients with RRMM, including those who relapsed from BCMA CAR-T therapy
- **Clinical Results**
  - Neutropenia and thrombocytopenia most frequent grade 3/4 adverse events
  - Additional adverse events include skin- and nail-related; dysgeusia/dysphagia; CRS; ICANS
  - 86% evaluable patients responded including 7 of 11 patients treated with prior BCMA-targeted treatment

---


---

Mezigdomide: A Cereblon E3 Ligase Modulator (CELMoD)

CELMoDs are related to the immunomodulatory drugs (IMiDs) but are more potent and may overcome resistance to IMiDs.

A phase 1/2 study of mezigdomide combined with dex in relapsed/refractory patients.

101 patients—who had received at least 6 prior lines of therapy and 100% were triple-class refractory (one-third were previously exposed to anti-BCMA therapy—received treatment with mezigdomide-dex.

A New Class of Drug: Immunocytokines

Immunocytokines are engineered to deliver cytokines (a protein produced by immune cells) that can prevent myeloma cells from dividing and to help boost myeloma-fighting immune cells.

Modakafusp alfa is an antibody that can bind to CD38 on myeloma cells that is fused to the cytokine interferon-alpha

100 patients who had a median of 7 prior lines of therapy were treated with different doses of modakafusp (19% had prior CAR T-cell therapy and 14% prior T cell engagers).

Overall response rate was 43% in patients receiving 1.5 mg/kg dose every 4 weeks (n=30); 27% of anti-BCMA exposed patients responded.


Key Points

- There is an ever increasing armamentarium of options in the relapsed setting of myeloma!
- There are many options in early relapse for patients progressing on lenalidomide maintenance. Isa-Kd has some of the best data in this area and can be administered in any practice.
- CAR T therapy continues to show impressive responses in later-line therapy and is now recapitulating that and more in earlier settings.
- Bispecific antibodies were stars of ASH 2022. Almost too many to keep on top of. Numerous targets and new strategies to optimize not only efficacy but toxicity.
- Prophylactic tocilizumab (and similar strategies) may be the key to getting bispecific antibodies into the community setting. Fixed-duration therapy is future of this approach…. ? The end to continuous therapy
Questions & Answers
MMRF Patient Resources

Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.
Patient Education Events

For information on new programs to take place in 2023, please visit themmrf.org/resources/education-program

Happy Holidays!
Thank you!